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(71) Applicant (for all designated States except US): CEL-GENE CORPORATION [US/US]; 7 Powder Horn Drive, Warren, NJ 07059 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): ZELDIS, Jerome, B. [—/—]; 157 Christopher Drive, Princeton, NJ 08540 (US).

(74) Agents: TSANG, Christopher, T. et al.; Jones Day, 222 East 41st Street, New York, NY 10164-3474 (US).

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(54) Title: METHODS OF USING AND COMPOSITIONS COMPRISING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR THE TREATMENT AND MANAGEMENT OF MYELOPROLIFERATIVE DISEASES

(57) Abstract: Methods of treating, preventing and/or managing a myeloproliferative disease are disclosed. Specific methods encompass the administration of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, alone or in combination with a second active agent, and/or the transplantation of blood or cells. Particular second active agent is capable of suppressing the overproduction of hematopoietic stem cells or ameliorating one or more of the symptoms of MPD. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US03/11325

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07D 209/34; A61K 38/21, 38/19  
US CL : 514/416; 424/85.7, 85.4

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 514/416; 424/85.7, 85.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,698,579 A (MULLER G.W.) 16 December 1997, see entire document.	1-7, 9-17, 22-24, 26-31
Y	SILVER, R. T. Interferon-Alpha 2b A New Treatment for Polycythemia Vera. Annals of Internal Medicine. 01 December 1993, Vol. 119, No. 11, pages 1091-1092, see entire document.	1-7, 9-17, 22-24, 26-31
Y	SCHANDENE et al. Interferon Alpha Prevents Spontaneous Apoptosis of Clonal Th2 Cells Associated with Chronic Hypereosinophilia. Blood. 15 December 2000, volume 96, No. 13, pages 42875-4292, see entire document.	1-7, 9-17, 22-24, 26-31
Y	HAO et al. Expression of Interferon Consensus Sequence Binding Protein (ICSBP) is Downregulated in Bcr-Abl-Induced Murine Chronic Myelogenous Leukemia-Like Disease, and forced Coexpression of ICSBP Inhibits Bcr-Abl-Induced Myeloproliferative Disorder. Molec. Cell. Biol. February 2000, Vol. 20, No. 4, pages 1149-1161, see entire document.	1-7, 9-17, 22-24, 26-31
Y	VACCA et al. Angiogenesis in Hematologic Malignancies. Haematologica. 12-14 November 2001, Vol. 86, Suppl 1 to No. 11, pages 1-5, see entire document.	1-7, 9-17, 22-24, 26-31



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
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Facsimile No. (703) 305-3230

Authorized officer

Jon P Weber, Ph.D.

Telephone No. 571-272-1600

## INTERNATIONAL SEARCH REPORT

## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CANEPA et al. Antitumor Activity of Thalidomide in Idopathic Myelofibrosis. Haematologica. 12-14 November 2001, Vol. 86, Suppl 1 to No. 11, pages 12-14, see entire document.	1-7, 9-17, 22-24, 26-31
Y	PRUNERI et al. Angiogenesis in Myelodysplastic Syndromes. Br. J. Cancer. 1999, Vol. 81, No. 8, pages 1398-1401.	1-7, 9-17, 22-24, 26-31
Y	LUNDBERG et al. Bone Marrow in Polycythemia Vera, Chronic Myelocytic Leukemia, and Myelofibrosis Has an Increased Vascularity. Am. J. Pathol. July 2000, Vol. 157, No. 1, pages 15-19.	1-7, 9-17, 22-24, 26-31

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US03/11325

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claim Nos.: 8,25,35 and 39  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
under Article 17(2)(b) because of defects under Article 17(2)(a).
  
3.  Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-7, 9-17, 22-24 and 26-31, interferon alpha and formula 1

Remark on Protest

  

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT****PCT/US03/11325****BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

I. Group 1, claim(s) 1-7, 9-17, 22-24, 26-31, first appearing cytokine inhibitor of Formula I, and first appearing second agent interferon-alpha, drawn to methods of treating, preventing or managing a myeloproliferative disease by administering a selective cytokine inhibitor.

Groups 2-11, and 11 more second agents (see claim 9).

Group 12, claim(s) 1-7, 9-15, 18-19, 22-24, 26-31, second appearing cytokine inhibitor of Formula II, and first appearing second agent interferon-alpha, drawn to methods of treating, preventing or managing a myeloproliferative disease by administering a selective cytokine inhibitor.

Groups 13-23, and 11 more second agents (see claim 9).

Group 24, claim(s) 1-7, 9-15, 20-24, 26-31, third appearing cytokine inhibitor of Formula III, and first appearing second agent interferon-alpha, drawn to methods of treating, preventing or managing a myeloproliferative disease by administering a selective cytokine inhibitor.

Groups 25-36, and 11 more second agents (see claim 9).

II. Group 37, claim(s) 32-34 and 36, and first appearing second agent interferon-alpha, drawn to a selective cytokine inhibitory composition.

Groups 37-48, and 11 more second agents (see claim 36).

III. Group 49, claim(s) 37-38, 40, drawn to a kit comprising a selective cytokine inhibitor and an agent that suppresses blood cell production.

IV. Group 50, claim(s) (39)-40, drawn to a kit comprising a selective cytokine inhibitor and any of numerous second agents.

**Continuation of B. FIELDS SEARCHED Item 3:****SCIRUS**

Search Terms: cytokine, inhibitor, myelo?